

Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Povarov Reaction Using Enecarbamates as Dienophiles: Highly Diastereo- and Enantioselective Synthesis of Substituted 4-Aminotetrahydroquinolines

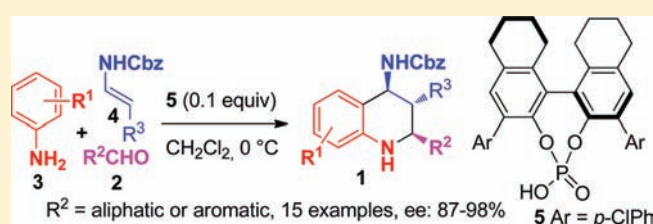
Guillaume Dagousset,[†] Jieping Zhu,^{*,‡} and Géraldine Masson^{*,†}

[†]Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

[‡]Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, CH-1015 Lausanne, Switzerland

S Supporting Information

ABSTRACT: A chiral phosphoric acid (**5**)-catalyzed three-component Povarov reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** afforded *cis*-4-amino-2-aryl(alkyl)-1,2,3,4-tetrahydroquinolines **1** in high yields with excellent diastereoselectivities (>95%) and almost complete enantioselectivities (up to >99% ee). The reaction was applicable to a wide range of anilines bearing electron-donating (OMe) and electron-withdrawing groups (e.g., Cl, CF₃, NO₂) and allowed, for the first time, aliphatic aldehydes to be employed in the enantioselective Povarov reaction. With β -substituted acyclic enecarbamates, 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines with three contiguous stereogenic centers were produced in excellent diastereo- and enantioselectivities (87 to >99% ee). A detailed study of the active catalytic species allowed us to reduce the catalyst loading from 10% to 0.5% with no deterioration of enantiomeric excess. In addition, mechanistic studies allowed us to conclude unequivocally that the Povarov reaction involving enecarbamate as dienophile proceeded via a stepwise mechanism. The key role of the free NH function of the enecarbamate in the success of this transformation was demonstrated. NMR experiments indicating the catalyst–substrate interaction as well as a linear correlation between catalyst and product ee's were also documented.



INTRODUCTION

Tetrahydroquinoline is a key structural unit found in many biologically active natural products¹ and synthetic pharmaceutical agents.^{1a,2} In particular, 4-amino-1,2,3,4-tetrahydroquinolines³ represent an important subclass of this family which has been found in natural products such as martinellin acid,⁴ a potent bradykinin antagonist. It has also displayed an excellent track record in medicinal chemistry, the notable examples being torcetrapib (CP-529,414, Pfizer),⁵ a potent and first cholesteryl ester transfer protein inhibitor, and (–)-L-689,560,⁶ a potent antagonist at the *N*-methyl-D-aspartate receptor glycine site (Figure 1).

Consequently, the development of new synthetic routes to tetrahydroquinolines has been actively investigated in recent years.⁷ Among many reported methods for the construction of polysubstituted tetrahydroquinolines, the Povarov reaction,⁸ an inverse electron-demand aza-Diels–Alder (IEDDA) reaction between 2-azadienes and electron-rich olefins catalyzed by either protic or Lewis acids, stood out as one of the most attractive. Since most of the tetrahydroquinoline-containing natural products and drug candidates contain stereogenic center(s), the ability to render the Povarov reaction enantioselective is of significant importance. However, despite efforts dedicated to this goal, the development of an enantioselective Povarov reaction met with only limited

success. Kobayashi⁹ and Sundararajan¹⁰ disclosed the first examples of enantioselective two-component Povarov reactions using chiral BINOL–ytterbium and aminodiol–titanium(IV) complexes, respectively, as catalysts. The enantioselectivities and application scope of these two catalytic processes were nevertheless moderate. A major breakthrough came from Akiyama's group, who documented a phosphoric acid-catalyzed enantioselective Povarov reaction of vinyl ethers and *N*-arylimines derived from *o*-hydroxyanilines. Although the Povarov adducts were generally obtained with excellent diastereoselectivities and enantiomeric excesses (ee's) under Akiyama's conditions, the necessity of using *o*-hydroxyaniline as one of the reaction partners limited the access to only 8-hydroxytetrahydroquinoline derivatives.¹¹ In addition, only imine-derived aromatic aldehydes were accepted as substrates in all these catalytic enantioselective processes.^{9,11}

In 2009, we reported the first example of a three-component enantioselective Povarov reaction for the synthesis of 4-amino-1,2,3,4-tetrahydroquinolines (**1**, Scheme 1). The reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** in the presence of a catalytic amount of chiral phosphoric acid **5** furnished

Received: June 24, 2011

Published: August 10, 2011

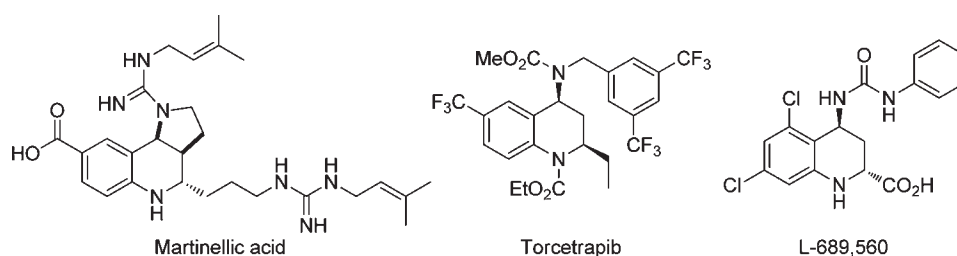
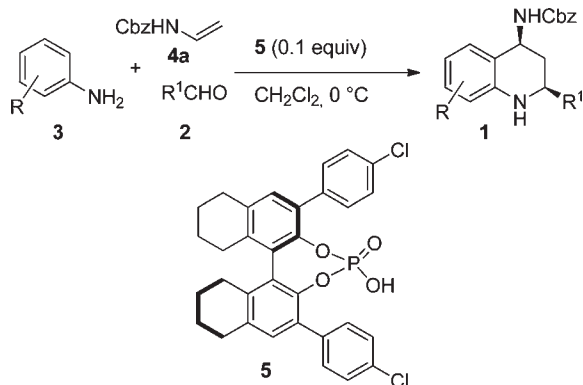


Figure 1. Selected examples of bioactive 4-aminotetrahydroquinolines.

Scheme 1. Catalytic Enantioselective Povarov Three-Component Synthesis of 2,4-Disubstituted 1,2,3,4-Tetrahydroquinolines

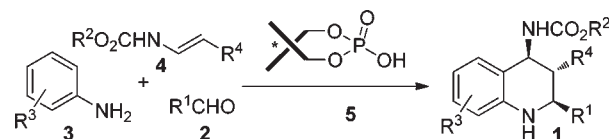


4-amino-1,2,3,4-tetrahydroquinolines **1** in good to high yields with excellent diastereo- (up to >99:1) and enantioselectivities (up to >99% ee).¹² Importantly, the aliphatic *N*-arylimines generated *in situ* were successfully employed in the enantioselective Povarov reaction for the first time. The use of benzyl *N*-vinylcarbamate (**4a**) possessing the free NH function as dienophile^{13,14} allowed us to use simple anilines, instead of *o*-hydroxyanilines, giving access to structurally diverse tetrahydroquinolines **1**.

Subsequent to our initial disclosure, Gong reported a three-component synthesis of the tricyclic ring system julolidine by combining the enantioselective Povarov reaction with the intramolecular hydroamination reaction.¹⁵ Ricci et al.¹⁶ and Feng et al.¹⁷ described two catalytic asymmetric IEDDA reactions employing vinylindoles and cyclopentadiene, respectively, as dienophiles. Jacobsen et al. developed an efficient asymmetric two-component Povarov reaction using 2,3-dihydrofuran, vinyl-lactam, and *N*-Cbz-2,3-dihydropyrrole as dienophiles in the presence of a dual chiral-achiral acid catalytic system.¹⁸

Despite this significant progress, enantioselective access to 2,3,4-trisubstituted tetrahydroquinolines via the Povarov reaction was restricted to cyclic dienophiles.^{9,17,18} To the best of our knowledge, there is no convenient method for the preparation of 4-amino-1,2,3,4-tetrahydroquinolines **1** with various substitution patterns at C-2, C-3, and C-4. In this paper, we briefly summarize our previous studies on the Brønsted acid-catalyzed enantioselective three-component Povarov reaction for the synthesis of highly substituted 4-aminotetrahydroquinolines. The use of β -substituted acyclic enecarbamates as a key reaction partner allowed us to access for the first time the enantiomerically enriched 2,3-disubstituted 4-amino-1,2,3,4-tetrahydroquinolines **1** (Scheme 2). We also detail control experiments, NMR titration

Scheme 2. Enantioselective Synthesis of 2,3,4-Trisubstituted 1,2,3,4-Tetrahydroquinolines

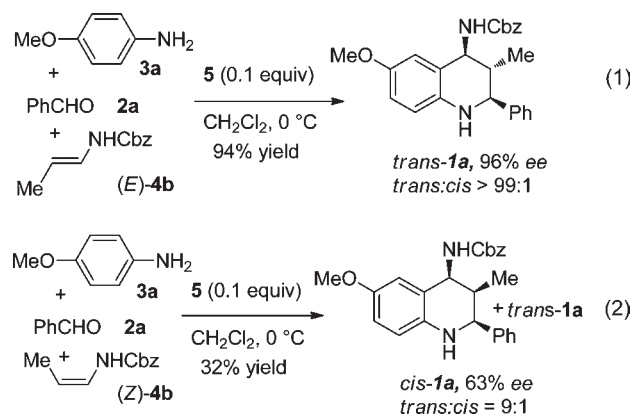


experiments, linear correlation between catalyst and product ee's, and mechanistic studies as well as a rationale for the stereochemical outcome of this transformation.

RESULTS AND DISCUSSION

In our preliminary communication, we demonstrated that the chiral phosphoric acid derived from octahydro-(*R*)-BINOL **5** (see Supporting Information for details) was able to efficiently promote the enantioselective three-component Povarov reaction between aldehydes **2**, anilines **3**, and benzyl *N*-vinylcarbamate (**4a**).^{8,19,20} A wide range of electron-neutral, -rich, and -poor aromatic aldehydes were appropriate substrates, affording *cis*-2,4-disubstituted 4-aminotetrahydroquinolines **1**²¹ with both high enantioselectivities (98 to >99% ee) and diastereoselectivities (>95:5 dr).¹² Remarkably, the optimized reaction conditions were also applicable to aliphatic aldehydes. Both α - and β -branched aldehydes participated effectively in the three-component reaction (Supporting Information). On the other hand, linear aldehydes gave lower yields due to the competitive isomerization of the *in situ* formed aliphatic *N*-arylimines to the corresponding enamines.^{4,22,24} However, we were pleased to find that when the reaction was carried out at -30 °C, the expected cycloadducts were isolated in good yields with high ee's (Supporting Information).¹² A wide range of anilines were also suitable partners to afford the corresponding cycloadducts in good to high yields and excellent enantioselectivities (up to 99% ee). However, in our previous report, when anilines with strong electron-withdrawing substituents such as 4-trifluoromethyl were subjected to the same conditions, moderate yields were observed. Thus, we decided to reinvestigate the reaction with 4-trifluoromethylaniline. Fortunately, by simply increasing the reaction time from 1 to 12 h, the yield of tetrahydroquinoline was significantly enhanced (Supporting Information). This modification increased the overall yield of our original synthesis of torcetrapib from 32 to 40%.¹²

Having succeeded in the elaboration of optically enriched *cis*-2,4-disubstituted-1,2,3,4-tetrahydroquinolines (see Supporting Information for details), we next investigated the use of β -substituted enecarbamates as nucleophiles in order to generate three adjacent stereogenic centers in one operation. As the

Scheme 3. Povarov Reaction of β -Substituted Acyclic Enecarbamates (*E*)-4b and (*Z*)-4b


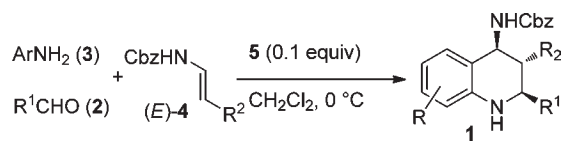
geometry of the dienophile can impact the stereochemical outcome of the reaction, we decided to test the benzylprop-1-enylcarbamates (*E*)-4b and (*Z*)-4b separately. Pleasingly, the three-component reaction using (*E*)-benzylprop-1-enylcarbamate (*E*)-4b, benzaldehyde (2a), and 4-methoxyaniline (3a) under our standard conditions afforded the desired tetrahydroquinoline (*trans*-1a, all-*trans*) in 94% yield with excellent enantio- and diastereoselectivity (eq 1, Scheme 3). On the other hand, the (*Z*)-enecarbamate (*Z*)-4b was much less reactive than its *E* counterpart, affording 1a in 32% yield as a mixture of two separable diastereoisomers (*trans*:*cis* = 9:1). Surprisingly, the major product isolated from the reaction of (*Z*)-4b was found to be the same (all-*trans*) as that derived from (*E*)-4b (eq 2, Scheme 3). We assumed that, in the presence of phosphoric acid, a slow *Z/E* isomerization of enecarbamate (*Z*)-4b to (*E*)-4b via the *N*-acyliminium intermediate occurred before the Mannich reaction. The subsequent reaction of (*E*)-4b with 2a and 3a gave *trans*-1a as a major product. It is also interesting to note that, while the *trans* isomer 1a was obtained in 90% ee, *cis*-1a was isolated in a much lower ee (63%). The *trans* relative stereochemistry between C-2 and C-3 and between C-3 and C-4 in 1a was established by NOESY experiments (Scheme 3).

Encouraged by the high levels of diastereo- and enantioselectivity observed in the reaction of (*E*)-4b, we next examined the scope of this reaction by varying the structure of aldehydes (Table 1). A variety of aromatic aldehydes, ranging from electron-rich substrates [3-methoxybenzaldehyde (2b), furaldehyde (2e)] to electron-poor aromatic aldehydes [4-nitrobenzaldehyde (2c)], underwent reaction with (*E*)-4b and 4-methoxyaniline (3a) without event to afford the corresponding tetrahydroquinolines in good yields with excellent enantioselectivities (entries 1, 2, and 4). *Ortho*-substituted aromatic aldehydes such as 2-bromobenzaldehyde (2d) and cinnamaldehyde (2f) required longer times (12 h) to drive the reaction to completion (entries 2 and 5). α -Substituted aliphatic aldehydes (entry 6) also performed well under the standard reaction conditions, although reactions with linear aldehydes (entries 7 and 8) had to be carried out at -30 °C to avoid undesired isomerization of the imine intermediate and enecarbamate.^{4,22,24} Anilines having electron-donating (4-methoxy), -neutral (H, entry 11, Table 1), and -withdrawing groups (4-nitro, entry 9) were suitable reaction partners to afford the corresponding adducts in high yields and excellent

enantioselectivities. As previously described,¹² when a *meta*-substituted aniline, such as 3-iodoaniline (3c, entry 10), was used, two regioisomers, 7-iodo-1k and 5-iodo-1k, were isolated, with the sterically more congested isomer 5-iodo-1k being the major one. To evaluate the influence of the substituent at the C-2 position of the double bond, a series of enecarbamates, bearing propyl (4c), isopropyl (4d), and *tert*-butyldiphenylsilyloxypropyl (4e) substituents, were prepared and were subjected to reaction with benzaldehyde (2a) and 4-methoxyaniline (3a) under our optimized conditions. With 4c and 4e, yields and selectivities were high and were comparable to those obtained with (*E*)-4b. A lower yield but still good enantioselectivity were obtained with the bulkier (*E*)-benzyl 3-methylbut-1-enylcarbamate 4d (entry 11).

Although the enantiomeric excess and yield were reliable, we found that time needed to complete the reaction varied (ranging from 1 to 12 h) depending on the batch of chiral phosphoric acid 5 used, as was observed earlier by Ding et al.²⁵ Recently Ishihara et al. and List et al. demonstrated that purification of chiral phosphoric acids by silica gel chromatography can result in the formation of a variable amount of alkali or alkaline earth metal-phosphoric acid complexes.²⁶ The formation of these phosphate salts could explain the variation of reaction rates in these chemical reactions. Indeed, when 5 washed with HCl was used, the 4-aminotetrahydroquinolines 1 were systematically obtained after 1 h.²⁷ As metal phosphate salts were known to create a well-defined chiral environment and could even, in certain cases, reverse the enantiofacial selectivities relative to the free phosphoric acids,²⁸ we decided to evaluate their catalytic power in the enantioselective Povarov reaction. Surprisingly, no reaction occurred when calcium bis(phosphate) complex Ca(5)₂, instead of 5, was used as catalyst under otherwise identical conditions. This demonstrated that only metal-free chiral phosphoric acid was an effective catalyst for the present Povarov reaction. On the basis of this observation, we reasoned that it might be possible to reduce the catalyst loadings without significantly affecting the catalytic activity and the enantioselectivity by using acid-washed phosphoric acid. The results are summarized in Table 2. It was found that, with 0.5 mol % of 5, reaction of 2a, 3a, and (*E*)-4b afforded 1a in 80% yield with 96% ee, albeit with a longer reaction time (12 h). In terms of operational convenience, the use of 2.5 mol % phosphoric acid 5 at 0 °C ensured high levels of reaction efficiency and enantioselectivity while maintaining the expedient reaction time.

The mechanism of the Povarov reaction has long been a topic of controversy.²⁹ Several recent theoretical studies indicated that the mechanism can be concerted or stepwise, depending on the dienophiles used. In our case, the polarized nature of the enecarbamate double bond led us to speculate that a stepwise mechanism initiated by the Mannich reaction might be predominant. If this pathway were indeed operating, it would then be possible to trap the *N*-acyliminium intermediate generated after the Mannich reaction by an external nucleophile. To verify this working hypothesis, a series of control experiments were performed. Reaction of benzaldehyde (2a), 4-methoxyaniline (3a), and enecarbamate 4a in the presence of 5 and EtOH (17 equiv) afforded indeed the Mannich adduct 6a in 21% yield, together with the tetrahydroquinoline 1 (50%). With aniline (3d) and electron-poor anilines such as 4-chloroaniline (3e) and 4-nitroaniline (3b) under otherwise identical conditions, only the Mannich adducts were isolated, at the expense of the Povarov products (Table 3). These results not only provided direct

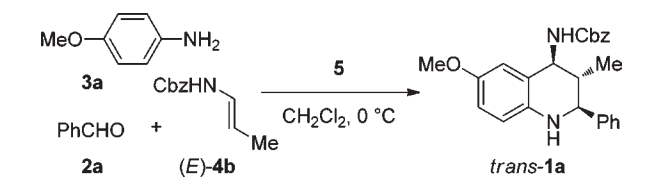
Table 1. Scope of the Enantioselective Brønsted Acid-Catalyzed Three-Component Povarov Reaction with β -Substituted (*E*)-Enecarbamates^a

entry	R ¹	Ar	(<i>E</i>)-4	1	yield (%) ^b	ee (%) ^c
1	<i>m</i> -MeOC ₆ H ₄ (2b)	3a	4b		87	97
2	<i>p</i> -NO ₂ C ₆ H ₄ (2c)	3a	4b		78	92
3	<i>o</i> -BrC ₆ H ₄ (2d)	3a	4b		78 ^d	98
4	2-Furyl (2e)	3a	4b		69	97
5	<i>E</i> -PhCH=CH ₂ (2f)	3a	4b		71 ^d	95
6	<i>c</i> C ₆ H ₁₁ (2g)	3a	4b		89	91
7	Et (2h)	3a	4b		82 ^{d,e}	96
8	BnOCH ₂ (2i)	3a	4b		72 ^{d,e}	96
9	2a	<i>p</i> -NO ₂ C ₆ H ₄ (3b)	4b		78	92

Table 1. Continued

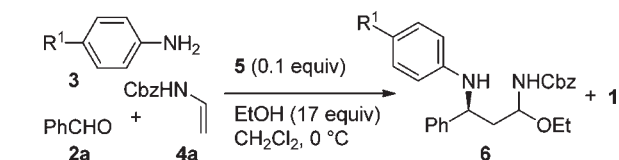
entry	R ¹	Ar	(<i>E</i>)-4	1	yield (%) ^b	ee (%) ^c
10	2a	<i>m</i> -IC ₆ H ₄ (3c)	4b	 1k-a (7-iodo) 1k-b (5-iodo)	15 (7-iodo) 66 (5-iodo)	98 92
11	2a	C ₆ H ₅ (3d)	4b	 1l	85	96
12	2a	3a	4c	 1m	84	96
13	2a	3a	4d	 1n	48	87
14	2a	3a	4e	 1o	97	93

^a General conditions: aldehyde (0.10 mmol), amine (0.10 mmol), β -substituted enecarbamate (0.11 mmol), and **5** (0.01 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C during 1 h. ^b Yields refer to chromatographically pure product. ^c Enantiomeric excess was determined by enantiodiscriminating HPLC analysis. ^d 12 h reaction time. ^e Reaction performed at -30 °C.

Table 2. Optimization of Catalyst Loading^a

entry	catalyst loading (mol %)	time (h)	yield (%) ^b	ee (%) ^c
1	10	1	94	96
2	2.50	3	78	96
3	1	12	81	96
4	0.5	12	80	96
5	0.1	72	16	96

^a General conditions: aldehyde (0.10 mmol), amine (0.10 mmol), benzyl *N*-vinylcarbamate (0.11 mmol), and **5** in CH₂Cl₂ (1.0 mL) at 0 °C. ^b Yields refer to chromatographically pure product. ^c Enantiomeric excess was determined by enantiodiscriminating HPLC analysis.

Table 3. Interrupted Povarov Cycloaddition^a

entry	R ¹	yield (%) ^b	
		6	1
1	MeO (3a)	21 (6a)	50
2	H (3d)	77 (6b)	11
3	Cl (3e)	85 (6c)	—
4	NO ₂ (3b)	72 (6d)	—

^a General conditions: aldehyde (0.10 mmol), amine (0.10 mmol), benzyl vinylcarbamate (0.11 mmol), ethanol (1.7 mmol), and **5** (0.01 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C. ^b Yields refer to chromatographically pure product.

evidence of a stepwise mechanism of our catalytic enantioselective Povarov reaction but also allowed us to develop an efficient enantioselective synthesis of 1,3-diamine via a one-pot Mannich reaction/reduction process.^{14f} The interrupted Povarov reaction was previously elegantly exploited by Lavilla and co-workers for the synthesis of heterocycles other than tetrahydroquinolines.³⁰

Dual activation of the imine and secondary enecarbamate by bifunctional chiral phosphoric acid catalysis was our working hypothesis for the development of the present transformation.^{12,14} To gain insight into this mechanistic assumption, we decided to evaluate the influence of the free NH function of carbamate on the enantioselectivity of the transformation. Tertiary enecarbamates such as benzyl *N*-methyl-*N*-vinylcarbamate (**4f**), 3-vinylloxazolidin-2-one (**4g**), and *N*-Cbz-2-pyrroline (**4h**) were synthesized and tested in the three-component reaction with **2a** and **3a** (Figure 2). With acyclic enecarbamates **4f** and **4g**, no reaction took place, while with the cyclic enecarbamate **4h**, the corresponding *endo* cycloadduct **1p** (dr >99/1) was isolated in 30% yield with only

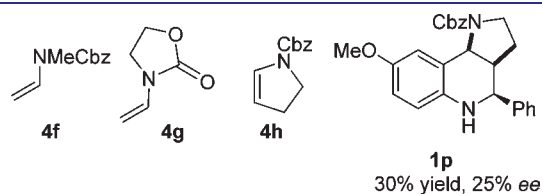


Figure 2. Povarov reaction of tertiary enecarbamates.

25% ee (Figure 2). These results indicated clearly that the NH moiety of **4a–e** plays an important role, not only for the enantioselectivity but also for the reactivity.³¹

To probe the nature of the catalyst–substrate interaction,^{32,33} titration of imine **7** with phosphoric acid by ¹H NMR spectroscopy was performed.³⁴ When 1 equiv of phosphoric acid **5** was used, a significant downfield shift of aldimine proton ($\Delta\delta = 1.6$ ppm) was observed, indicating the association of these two species (Figure 3).³⁵ When 2 equiv of phosphoric acid **5** was used, **7** was found to exist as a single associated form, **5-7**. Recent NMR studies from Gschwind, Rueping and co-workers using ¹⁵N-labeled imines concluded that, while ion-pairing is the predominant interaction between diphenylphosphate and (*E*)-*N*-(4-methylbenzylidene)aniline, H-bonding between imines (especially those with less basic one) and phosphoric acids could also contribute to the activation of imines.³⁶ While our titration experiments could not allow us to distinguish these two activation modes, we would favor the ion-pairing activation mode in our case on the basis of the fact that imine **7** has a basic nitrogen atom. This hypothesis was also reinforced by the absence of a nonlinear effect under our conditions (*vide infra*).

Gong and co-workers recently demonstrated that phosphoric acids can exist as aggregates both in solution and in the solid state.³⁷ They also provided evidence of asymmetric amplification of certain phosphoric acid-catalyzed reactions, especially those involving nonbasic *N*-acylated imines as electrophiles. This observation prompted us to investigate the relationship between the optical purity of the phosphoric acid catalyst **5** and that of the

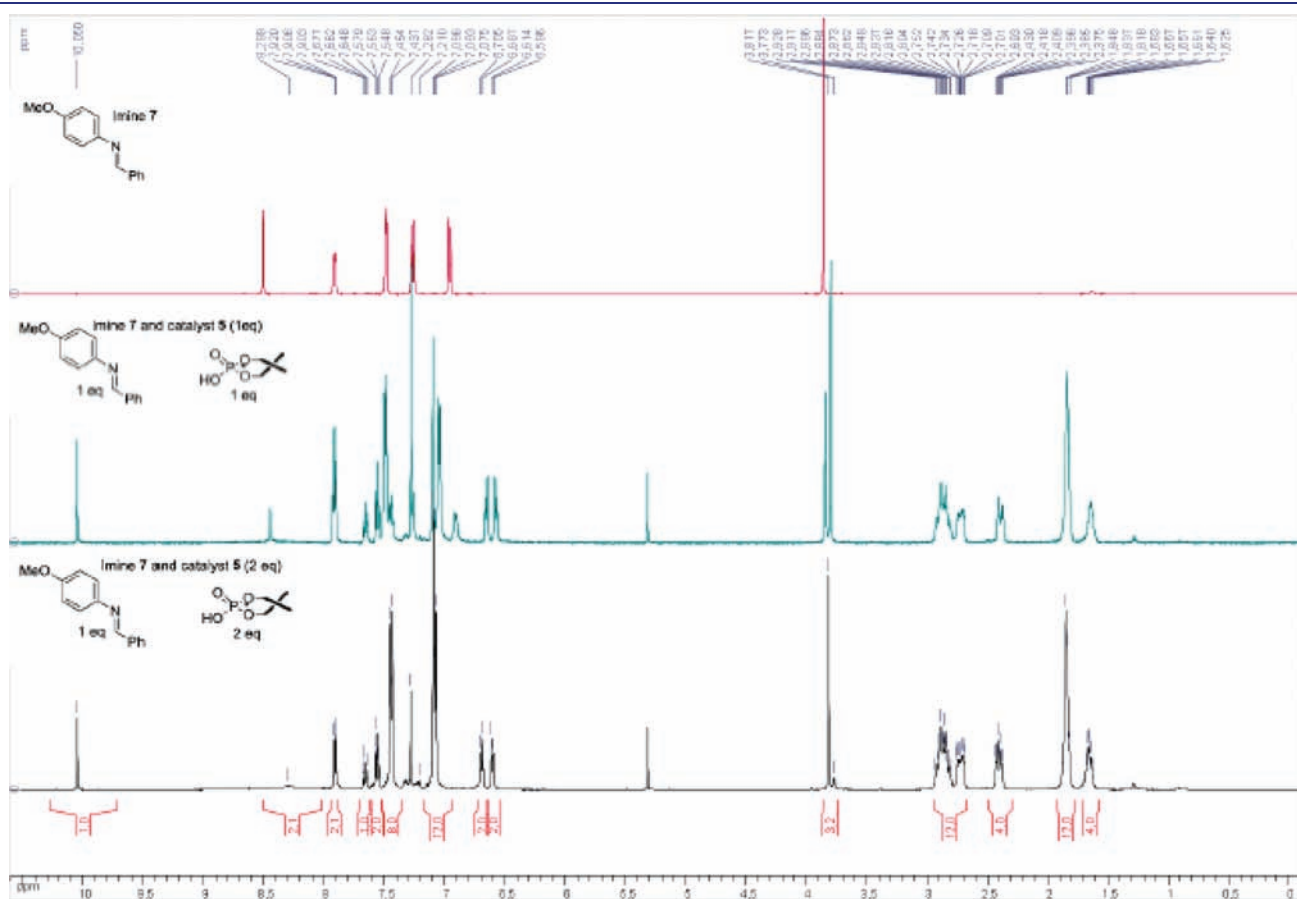


Figure 3. NMR spectra of titration experiments (500 MHz, CDCl₃).

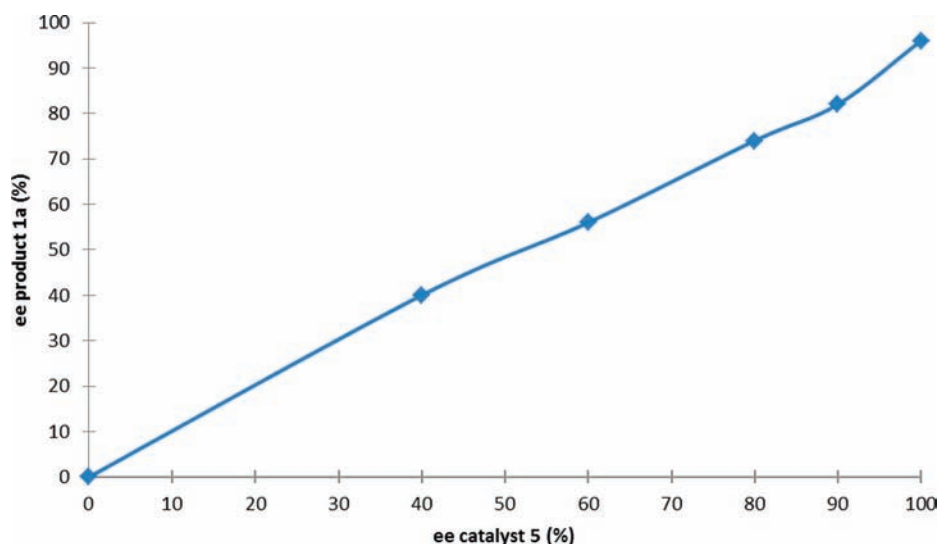
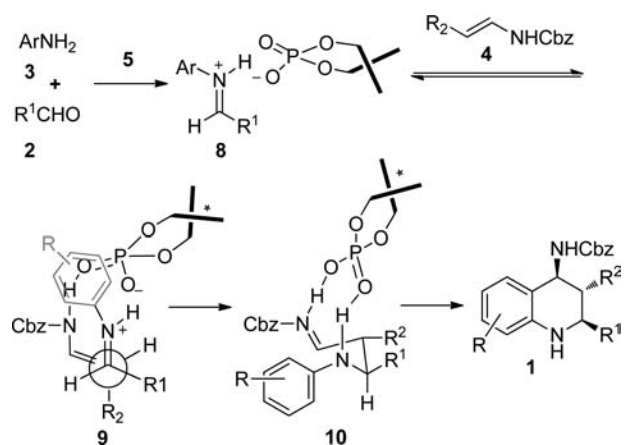


Figure 4. Correlation between the enantiomeric excess of **5** and that of product *trans*-**1a**.

Scheme 4. Proposed Mechanism and Stereochemical Issue



tetrahydroquinoline *trans*-**1a** under our optimal conditions. As shown in Figure 4, the ee of the tetrahydroquinoline *trans*-**1a** is nearly proportional to that of the chiral phosphoric acid **5**, indicating the absence of a nonlinear effect.³⁸ We therefore assumed that a single catalyst molecule was involved in the activation of imine in the key Mannich addition step.

On the basis of these observations, we assumed that the phosphoric acid-catalyzed three-component Povarov reaction proceeded via protonation of the imine, forming chiral ion pair **8**, followed by hydrogen-bonding between the enecarbamate NH and the Lewis basic phosphoryl oxygen. A pseudo-intramolecular *Si*-face attack of (*E*)-enecarbamate on the iminium carbon of the chiral contact ion pairs via transition state **9** would then afford iminium **10**, with concurrent proton shift within the phosphoric acid sphere. Finally, an intramolecular aza-Friedel–Crafts reaction via the sterically less congested conformer **10** would furnish the observed 2,4-*cis*-substituted tetrahydroquinoline **1** with defined absolute configuration, as shown in Scheme 4. It is interesting to note that the absolute configuration of tetrahydroquinoline **1** we obtained is different from that obtained by Akiyama, although the chiral phosphoric acids used in both cases

Scheme 5. Akiyama's Stereochemical Model

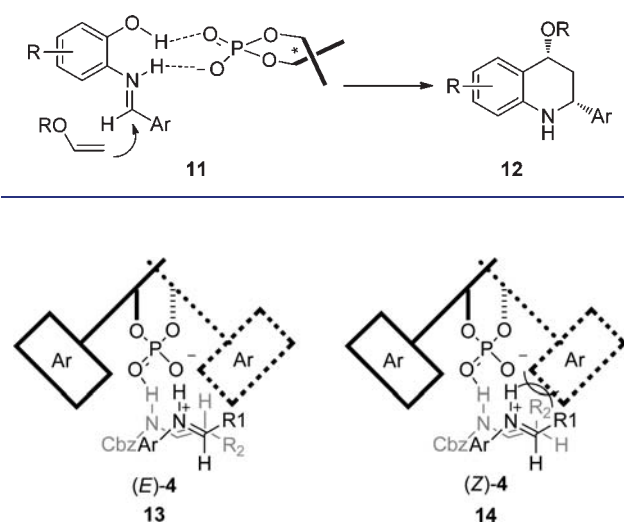


Figure 5. Simón and Goodman's model.

were derived from (*R*)-BINOL. The reversal of enantiofacial selectivity could be accounted for by the difference in H-bonding models. In Akiyama's catalytic system, the phosphoric acid activated only the electrophile via the participation of the *o*-hydroxy group.¹¹ The *Re*-face attack of the enol ether onto imine via transition state **11** would then afford the tetrahydroquinoline **12** (Scheme 5).

Evidence that both activation modes via transition states **9** and **11** could be operating was obtained by using the *o*-hydroxyaniline (**3e**) in the Povarov reaction. Reaction of **3e** with benzaldehyde (**2a**) and enecarbamate **4a** afforded the corresponding tetrahydroquinoline **1q** in 64% yield with 71% ee. A possible competition between our dual activation model and Akiyama's model could account for the diminished ee of product **1q**.

On the basis of the results of their DFT calculation, Simón and Goodman proposed a model, **13**, to account for the stereochemical outcome of the Mannich reaction that we observed experimentally

(Figure 5).^{39,40} Although the significant difference in the reactivity observed between *Z*- and *E*-isomers **4b** has yet to be explained, a transition state, **14** (Figure 5), displaying unfavorable interactions between the (*Z*)-enecarbamate and the ion-pair complex of the imine and **5**, could potentially explain the low reactivity of the (*Z*)-enecarbamate.

CONCLUSION

We reported the first catalytic enantioselective three-component Povarov reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** to furnish *cis*-1-aryl(alkyl)-4-aminotetrahydroquinolines **1** in good yields with excellent diastereo- and enantioselectivities (up to 98% ee). The use of acyclic β -substituted enecarbamates in this reaction allowed us to access the 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines with three contiguous stereogenic centers, again with high diastereoselectivities and excellent enantioselectivities. A study on active catalytic species demonstrated that only the free phosphoric acid catalyzed the Povarov reaction. These findings allowed us to reduce the catalyst loading by a factor of 20, to as little as 0.5 mol %. The trapping experiments provided sound evidence that the present Povarov reaction involving enecarbamate proceeded via a stepwise mechanism. Mechanistic investigations including NMR spectroscopy studies, linear effects, and control experiments highlighted the crucial role played by the activation of the imine via ion-pairing and the enecarbamate via H-bonding with bifunctional phosphoric acid catalyst. The low catalyst loading, excellent yields and enantioselectivities, and operational simplicity make our catalytic system attractive for the synthesis of highly functionalized, enantiomerically enriched 4-aminotetrahydroquinolines.

EXPERIMENTAL SECTION

General Procedure for the Catalytic Enantioselective Three-Component Povarov Reaction. To a solution of aldehyde (**2**, 0.1 mmol) in dry CH₂Cl₂ (0.4 mL) at room temperature was added aniline (**3**, 0.1 mmol). After being stirred at room temperature for 30 min, the reaction mixture was cooled to 0 °C, and a solution of phosphoric acid catalyst (**5**, 0.01 mmol) and enecarbamate (**4**, 0.11 mmol) in CH₂Cl₂ (0.3 mL) was added. The resulting solution was stirred under an argon atmosphere at 0 °C for 1 h. Solvents were removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (heptane/EtOAc) to afford the corresponding 4-amino-1,2,3,4-tetrahydroquinoline.

ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization of new compounds, and selected NMR and HPLC spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

jiaping.zhu@epfl.ch; masson@icsn.cnrs-gif.fr

ACKNOWLEDGMENT

We thank CNRS for financial support. G.D. thanks MESR for a doctoral fellowship.

REFERENCES

- (1) Selected review: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. Selected examples: (b) Omura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiot.* **1980**, *33*, 1395. (c) Copp, B. R.; Fulton, K. F.; Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1994**, *59*, 8233. (d) Jacquemond-Collet, I.; Benoit-Vical, F.; Mustofa; Valentin, A.; Stanislas, E.; Mallié, M.; Fourasté, I. *Planta Med.* **2002**, *68*, 68. (e) Wallace, O. B.; Lauwers, K. S.; Jones, S. A.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907. (f) Di Fabio, R.; Tranquillini, E.; Bertani, B.; Alvaro, G.; Micheli, F.; Sabbatini, F.; Pizzi, M. D.; Pentassuglia, G.; Pasquarello, A.; Messeri, T.; Donati, D.; Ratti, E.; Arban, R.; Dal Forno, G.; Reggiani, A.; Barnaby, R. *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 3863. (g) Avemaria, F.; Vanderheiden, S.; Bräse, S. *Tetrahedron* **2003**, *59*, 6785. (h) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015. (i) Asolkar, R. N.; Schroeder, D.; Heckmann, R.; Lang, S.; Wagner-Doebler, I.; Laatsch, H. *J. Antibiot.* **2004**, *57*, 17. (j) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069. (k) Morehouse, L. A.; Sugarman, E. D.; Bourassa, P.-A.; Sang, T. M.; Zimetti, F.; Gao, F.; Rothblat, G. H.; Milici, A. J. *J. Lipid Res.* **2007**, *48*, 1263. (l) Rano, T. A.; McMaster, E. S.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2456. (m) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.* **2011**, *13*, 65.
- (2) Representative examples: (a) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. (c) Hanada, K.; Furuya, K.; Inoguchi, K.; Miyakawa, M.; Nagata, N. Int. Patent WO 0127086, 2001; *Chem. Abstr.* **2001**, *134*, 295752.
- (3) Bazin, M.; Kuhn, C. *J. Comb. Chem.* **2005**, *7*, 302 and references therein.
- (4) (a) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215. (b) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405. (c) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913.
- (5) (a) Damon, D. B.; Dugger, R. W. Eur. Pat. Appl. EP1125929, 2001, and U.S. Patent 6,313,142, 2001. (b) Damon, D. B.; Dugger, R. W.; Scott, R. W. U.S. Patent 6,689,897, 2004. (c) Damon, D. B.; Dugger, R. W.; Magnus-Aryitey, G.; Ruggeri, R. B.; Wester, R. T.; Tu, M.; Abramov, Y. *Org. Process Res. Dev.* **2006**, *10*, 464. (d) Damon, D. B.; Dugger, R. W.; Hubbs, S. E.; Scott, J. M.; Scott, R. W. *Org. Process Res. Dev.* **2006**, *10*, 472.
- (6) (a) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. *J. Med. Chem.* **1992**, *35*, 1954. (b) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65.
- (7) Examples of selective C–H bond functionalization via a hydride shift/cyclization sequence: (a) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (b) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (c) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600. (d) Zhou, G.; Liu, F.; Zhang, J. *Chem.—Eur. J.* **2011**, *17*, 3101. (e) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. Reduction of quinolone, selected examples: (f) Deport, C.; Buchotte, M.; Abecassis, K.; Tadaoka, H.; Ayad, T.; Ohshima, T.; Genet, J.-P.; Mashima, K.; Ratovelomanana-Vidal, V. *Synlett* **2007**, 2743. (g) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (h) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (i) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759. (j) Dobereiner, G. E.; Nova, A.; Schley, N. D.; Hazari, N.; Miller, S. J.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7547. (k) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878. Michael addition, selected examples: (l) Guin, M.; Phua,

- P. H.; Caille, J.-C.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 6290. (m) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959. (n) Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett.* **2011**, *13*, 832. Reissert-type reaction: (o) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801.
- (8) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. General review of imino Diels–Alder reactions: (b) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
- (9) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.
- (10) Sundararajan, G.; Prabakaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.
- (11) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.
- (12) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598.
- (13) Selected reviews dealing with enamides (or enecarbamates) as nucleophiles: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (c) Carbery, D. R. *Org. Bioorg. Chem.* **2008**, *6*, 3455. (d) Nugenta, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (e) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599.
- (14) Selected examples of using enamides (or enecarbamates) as nucleophiles in phosphoric acid-catalyzed transformations: (a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (d) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553. (e) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4620. (f) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546. (g) Lu, M.; Lu, Y.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588.
- (15) (a) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266. (b) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, in press (DOI: 10.1021/ar2000343).
- (16) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327.
- (17) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799.
- (18) (a) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.
- (19) Recent reviews on Brønsted acid catalysis: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. Recent reviews on chiral phosphoric acid catalysis: (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (e) Terada, M. *Chem. Commun.* **2008**, 4097. (f) Terada, M. *Synthesis* **2010**, 1929. (g) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (h) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395.
- (20) Seminal reports on the use of BINOL-derived phosphoric acids in enantioselective transformations: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
- (21) The 2,4-*cis* relative stereochemistry of **1** was assigned by analysis of the ¹H NMR spectra recorded in MeOH-*d*₄: Funabashi, M.; Iwakawa, J.; Yoshimura *Bull. Soc. Chim. Jpn.* **1969**, *42*, 2885.
- (22) Encarbamates (enamides) as imine surrogates in the presence of phosphoric acid: (a) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. (b) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637. (c) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452. Encarbamates (enamides) as imine surrogates in the presence of Lewis acid: (d) Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, H.; Matsubara, R. *Org. Lett.* **2006**, *8*, 4923.
- (23) (a) Seayad, J.; List, B. Catalytic Asymmetric Multicomponent Reactions. In *Multicomponent Reaction*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; p 227. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (e) Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. *Chem.—Eur. J.* **2007**, *13*, 8920.
- (24) (a) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855. (b) Katritzky, A.; Rachwak, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 3993. (c) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287. (d) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462. (e) Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009. (f) Talukdar, S.; Chen, C.-T.; Fang, J.-M. *J. Org. Chem.* **2000**, *65*, 3148. (g) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362. (h) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Madhuri, C.; Ramalingam, T. *Synlett* **2001**, 240. (i) Lavilla, R.; Bernadeu, M. C.; Carranco, I.; Díaz, J. L. *Org. Lett.* **2003**, *5*, 717. (j) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569. (k) Legros, J.; Crousse, B.; Ourévitich, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899. (l) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977.
- (25) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840.
- (26) (a) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823. (b) Klusmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189. Example of a phosphoramidate/calcium complex: (c) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (d) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem.—Eur. J.* **2010**, *16*, 13116.
- (27) Except for the specified examples, which normally required longer reaction times.
- (28) Selected examples of using phosphate metal salt in enantioselective transformations: (a) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776. (b) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 8396. (c) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, P. *Org. Lett.* **2010**, *12*, 1096. (d) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem.—Eur. J.* **2010**, *16*, 13116. (e) Ingle, G. K.; Liang, Y.; Mormino, M. G.; Li, G.; Fronczek, F. R.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2054. (f) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339. (g) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188. (h) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135. (i) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94. (j) Rueping, M.; Bootwicha, T.; Sugiono, E. *Synlett* **2011**, 323. (k) Terada, M.; Kanomata, K. *Synlett* **2011**, 1255. Recent reviews: (l) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (m) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. General review on calcium complex in homogeneous catalysis: (n) Harder, S. *Chem. Rev.* **2010**, *110*, 3852.
- (29) Stepwise mechanism: (a) Kobayashi, S.; Ishitani, H.; Nakagawa, S. *Synthesis* **1995**, 1195. (b) Hermitage, S.; Jayb, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633. (c) Stevenson, P. J.; Graham, I. *Arkivoc* **2003**, 139. (d) Carranco, I.; Díaz, J. L.; Jiménez, O.; Lavilla, R. *Tetrahedron Lett.* **2003**, *44*, 8449. (e) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synthesis* **2008**, 1039. (f) Alves, M. J.; Azoia, N. G.; Fortes, A. G. *Tetrahedron* **2007**, *63*, 727. (g) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451. Concerted mechanism: (h) Beifuss, U.; Ledderhose, S.; Ondrus, V. *Arkivoc* **2005**, 147. (i) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Arkivoc* **2007**, 12. See also: (j) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330. (k) Whiting, A.; Windsor, C. M. *Tetrahedron* **1998**, *54*, 6035. An excellent review on the mechanistic aspects of multicomponent Povarov reactions: (l) Bello, D.; Ramón, Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332.
- (30) (a) Jiménez, O.; de la Rosa, G.; Lavilla, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6521. (b) Isambert, N.; Cruz, M.; Arévalo, M. J.; Gómez, E.; Lavilla, R. *Org. Lett.* **2007**, *9*, 4199. (c) Bernardi, L.; Comes-Franchini, M.; Fochi, M.; Leo, V.; Mazzanti, A.; Ricci, A. *Adv. Synth. Catal.* **2010**, *352*, 3399.
- (31) Tertiary enamides as nucleophiles: Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390.

(32) (a) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520. (b) Pregosin, P. S. *Pure Appl. Chem.* **2009**, *81*, 615.

(33) Mechanistic studies by mass spectroscopy: Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1463.

(34) NMR spectroscopic studies on protonated imines: (a) Sharma, G. M.; Roels, O. A. *J. Org. Chem.* **1973**, *38*, 3648. (b) Bissonnetteh, M.; Le Thanh, H.; Vocelle, D. *Can. J. Chem.* **1985**, *63*, 2298. (c) Knorr, R.; Ferchland, K. *Liebigs Ann.* **1995**, 419.

(35) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717.

(36) Fleischmann, M.; Drettwan, D.; Sugiono, E.; Rueping, M.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6364.

(37) Li, N.; Chen, X.-H.; Zhou, S.-M.; Luo, S.-W.; Song, J.; Ren, L.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 6378.

(38) Satyanarayana, T.; Abrahm, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456.

(39) Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

(40) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölcüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042.